PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/002714	24.06.2004	24.06.2003

International Patent Classification (IPC) or both national classification and IPC
C07D311/20, A61K31/353

Applicant
GW PHARMA LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/002714

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 14,15 in respect of industrial applicability

because:

☒ the said international application, or the said claims Nos. 14,15 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-18
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-18
Industrial applicability (IA)	Yes:	Claims	1-13,16-18
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

III

For the assessment of the present claims 14 and 15. on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims14 and 15 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

V and VI

Reference is made to the following documents:

D1: WO 02/26728 A (IMMUGEN PHARMACEUTICALS INC ; TRAVIS CRAIG R (US)) 4 April 2002 (2002-04-04)

D2: WO 2004/016254 A (IMMUGEN PHARMACEUTICALS INC ; TRAVIS CRAIG R (US)) 26 February 2004 (2004-02-26)

D3: US-A-4 837 228 (ELSOHLY MAHMOUD ET AL) 6 June 1989 (1989-06-06)

D4: US 2003/232101 A1 (TRAVIS CRAIG R) 18 December 2003 (2003-12-18)
D1: US-B-6 328 9921 (BROOKE LAWRENCE L ET AL) 11 December 2001 (2001-12-11)

D5: GAONI Y ET AL: "THE ISOLATION AND STRUCTURE OF 1-TETRAHYDROCANNABINOL AND OTHER NEUTRAL CANNABINOIDS FROM HASHISH" 1971, JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, PAGE(S) 217-224 , XP001095011 ISSN: 0002-7863

D6: CA-2 322 549 (SUTHERLAND MARTIN D ; HORNBY A PAUL (CA); DIMOTOFF PAVEL U (CA)) 27 March 2002 (2002-03-27)

D7: US-B-6 328 9921 (BROOKE LAWRENCE L ET AL) 11 December 2001 (2001-12-11)

Novelty

The compound of example 10 differs from those of formula 1 according to claim 1 of the application through the length of the R^3 group. However the claims include derivatives of the compounds of formula 1, such that this example together with the disclosures on page 9, lines 19- page 14, line 16 is novelty destroying to the present claim.

The claims of D1 include both compounds overlapping directly with the compounds of formula 1 in the present claims as well as compounds which anticipate derivatives of the formula 1 compounds. This together with disclosures of pharmaceutical compositions of these compounds (see above paragraph and claim 13) is novelty destroying to the present claims.

The pharmaceutical compositions of D1 may also be formulated e.g. for topical formulations (see page 10, 2nd para of D1), such that claim 11 is also not novel.

The compositions of D1 also include antianxiety agents associated with mental depression (see page 13 of D1), such that claim 13 to 17 are anticipated by D1.

The compounds of formula 1 in the present differ from those of claim 1 D3 in that they are chroman type compounds, whereas the compounds of claim 1 of D3 are chromene. derivatives (see double bond in the six membered oxygen containing ring). In this respect however the lack of clarity objection concerning whether the formula 1 compounds are intended to include chromen derivatives in section VIII is to be noted.

Since, the compounds of formula 1 of the present claims also include derivatives, the present claims are considered to be anticipated by claim 1 of D3. Derivatives would also include unsaturated forms of the compounds of formula 1.

Compounds (IV) and (X) (column 3 of D3) together with the disclosure in column 3, lines 19-36 of column D3 is novelty destroying to the present claims.
Table I of D5 shows the components of hashish includes cannabichromene, This together with the fact that cannabis has been used as a medicine (see first paragraph of D5) results in the disclosures of D5 being novelty destryoing to the present claims.

D7 discloses that cannabis contains cannabichromene (see column 1, lines 23-26. and column 2, line 45 -53) and lists certain medicinal uses of cananabbis including depression and further a method of treating a patient with a transdermal cannabis preparation. These disclosures are novelty destroying to the present claims). Similarly D6, which disclose the use of cannabis in treating depression and anxiety is considered to be novelty destroying to the present claims.

Inventive Step

D7 is considered to be the closest prior art.

In view of the disclosures of D6 or D7, it is considered that the skilled person could have readily arrived at the claimed compositions, in particular he /she would have expected the claimed compositions to be useful in the treatment of mood disorders and depression.

The problem underlying the application is therefore conbsidered to be the provision of compositions having surprising effect compared to the closest prior art.

In the absence of any surprising effect with respect to D6 an inventive step cannot be acknowledged.

certain cited documents

For the purposes of this communication it has been assumed that the priority of the present application is valid.

D2 and D5 do not constitute prior art within the meaning of Rule 64.1 (b).

VIII

A) The term "derivative" indicated in the claims leads to an unclear scope of claim intended.

The term "derivative" in connection with compounds includes compounds obtained from another compound by a chemical reaction.Therefore compounds of formula 1 in the claims include open forms, structures which are structurally remote from

the compounds of formul a 1, functional dervatives, compounds wherein the heteroatoms are exchanged by alternative atoms, compounds with numerous different types of side groups etc.

Having regard for the desired activities it is not considered that that all such derivatives would have the desired activities and that it is intended to claim all such structures. It remains unclear which actual structures are being claimed and where the borders lies.

B) In the description on page 4, the following has been indicated "the cannabichromene or canabichromene type compounds" of formula 1 included in the invention may be naturally occurring or synthetic compounds.

It is further indicated "Natural cannabichromenes include cannabichromene (CBC) Formula 2) and cannabichromene propyl analogue (CBC-V) (formula 3)".

Inspection of formula 1 (see also the claims) and formulae 2 and 3 shows that they are not actually cannabichromene or cannabichromene type compounds, since a double bond is missing in the 6-membered oxygen containing fused ring. In this respect the correct structure of cannabichromene is given in D5, page 218, column 1, formula Va (cf double bond between positions 7 and 8).

It is therefore unclear, whether there is an error in the depiction of the claimed compounds.

C) It is considered to be unclear, which compositions in claim 1 are excluded by the expression "smoked cannabis".